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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/774,278	01/30/2001	Gregory M. Lanza	4375-000004/US	2535
28997	7590	03/09/2004	EXAMINER	
HARNES, DICKEY, & PIERCE, P.L.C			SHARAREH, SHAHNAM J	
7700 BONHOMME, STE 400				
ST. LOUIS, MO 63105			ART UNIT	PAPER NUMBER

1617

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/774,278

Applicant(s)

LANZA ET AL.

Examiner

Shahnam Sharareh

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 December 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,7,8,13,17,18,21,25,26,31,35 and 68-77 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3,7,8,13,17,18,21,25,26,31,35 and 68-77 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 8, 2003 and October 2003 has been entered.

Any rejection that is not addressed in this Office Action is considered obviated in view of the amendments made to the pending claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 7-8, 13, 17-18, 21, 25-26, 31, 35, 68-77 rejected under 35

U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 18 recites limitations that lack sufficient antecedent basis. Claim 1 recites the limitation "the bound nanoparticles" in line 3 and "liquid nanoparticles" in line 4 of the claims. There is insufficient antecedent basis for these limitations in the claim. Claim 18 recites the limitation "the liquid nanoparticles bound to said target.." in line 3 of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 7-8, 13, 17-18, 25-26, 31, 35, 68-72, 74, 76-77 are rejected under 35 U.S.C. 102(e) as being anticipated by Ostensen US Patent 6,375,931.

The instant claims are directed to methods of enhancing and measuring acoustic reflectivity of a target for Ultrasound Imaging comprising measuring reflectivity prior to raising the temperature of the bound nanoparticles, raising the temperature of said nanoparticles, measuring reflectivity after said rise of temperature and determining the change in reflectivity of the nanoparticles before and after the raising of the temperature.

Accordingly, Examiner interprets the pending claims to be directed to methods of performing ultrasound imaging comprising having bound nanoparticles in a target area,

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measuring reflectivity of said bound nanoparticles, raising the temperature of the bound nanoparticles, measuring the reflectivity of the bound nanoparticles after said raising of the temperature, and determining the change in reflectivity. Note that such recitations, as “enhancing and measuring acoustic reflectivity” are viewed to be inherent in any methods of ultrasound imaging that performs the instantly claimed method steps.

Examiner takes the position that the continuous ultrasound imaging performed by Ostensen on a specific site inherently meets the process step limitations of the instant claims for the following reasons. Therefore, the instant limitation of “enhancing and measuring acoustic reflectivity” is also anticipated by Ostensen.

Ostensen discloses methods of performing ultrasound imaging comprising administering a perfluorocarbon emulsion comprising such perfluorocarbons as perfluoropentane, perfluorohexane, and even perfluorooctane to a specific region of a patient (see abstract, col 8, lines 1-60). Ostensen teaches droplets that are smaller than 10 μm and thus meets the limitations of the instant nanoparticles, because the sizes of the instant nanoparticles as described in page 21, line 7-10 of the specification encompass particles as large as 10 μm . (see 9, lines 34-38; col 35-37, and claim 4 wherein various perfluorocarbon emulsion mixtures are described).

Example 5 and 10 of Ostensen describes Ostensen’s process steps wherein a perfluorocarbon emulsion is administered to a mammal. Ostensen then teaches imaging of a specific site such as heart or kidney. Ostensen specifically expresses a steady rise in enhancement of the contrast images (see col 39-40). As described by Ostensen, this steady rise of resonance intensity is attributed to an increase in microbubble size which

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is respectively caused by an increase in temperature of at least 5 Deg C of the perfluorocarbon liquid within the microbubbles of Ostensen. Note that Ostensen states in col 35, line 10:

Analysis of the perfluorobutane gas dispersion alone showed that at 9° C. 52% of the microbubbles were of size below 9.9 µm; this proportion was reduced to 31% when the temperature had increased to 37° C. This temperature change was accompanied by a corresponding increase in the proportion of microbubbles in the size range 15-50 µm, from 8% to 42%.

Therefore, given the fact that perfluorobutane, perfluoropentane, perfluorohexane, and perfluoroheptanes are liquid at room temperature, and that microparticles containing such compounds increase in size when subject to ultrasound frequency as described above, the Examiner takes the position that the continuous ultrasound imaging over a period of time of a specific site, as described by Ostensen, is essentially a measurement of the change in reflectivity of contrast microbubbles wherein the size of these microbubbles are increased subsequent to a rise of temperature, because the intensity of contrast increases with the duration of exposure to the ultrasound frequency.

Further, Ostensen discloses the use of targeted microbubbles comprising an RGD ligand that are specific for myocardium. Thus, specific bounding of such targeted microbubbles to the myocardium in example 24 is presumed. (see examples 24 and 10, 1 (az)). Therefore, such sequence of steps described in Ostensen's patent meet the steps (a)-(d) of the instant claim 1.

Finally, Ostensen teaches the use of various therapeutic agents with his contrast agents. (see col 17-18, claims 22-27). Accordingly, Ostensen's methods either expressly or inherently anticipate the limitations of the instant claims when Ostensen

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performs a continuous ultrasound imaging from a sited that is exposed to a targeted microbubble.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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Claims 1, 3, 7-8, 13, 17-18, 21, 25-26, 31, 35, 68-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ostensen.

The teachings of Ostensen are described above. Ostensen teaches the use of perfluorooctane, but fails to exemplify it. Ostensen also fails to administer his emulsion system to a human.

Nevertheless, Ostensen provides adequate support for the use of any perfluorocarbon. Further, Ostensen administers his contrast agents to dogs, which are well recognized animal models for humans. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to modify Ostensen's method and employ other art equivalent perfluorocarbon liquids such as perfluorooctane, in humans because the ordinary skill in the art would have had a reasonable expectation of success in observing optimal clinical results in humans as evident in dogs.

Response to Arguments

Applicant's arguments filed on October 2003 have been considered but are moot in view of the new grounds of rejection. However, Examiner would address the following issue as it may be applicable to the new grounds of rejection.

Applicant argued that the cited prior art (Unger) merely expose the surrounding tissues to the ultrasound energy and never measures the reflectivity of the liquid nanoparticles. In response, Examiner states that first of all the instant claims does not exclude exposure of ultrasound energy to the surrounding tissues. Nevertheless, once the surrounding tissues are exposed to the ultrasound energy, the nanoparticles within the tissue are also exposed to said energy, therefore, the rise of temperature secondary

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to the exposure to ultrasound energy is inherent once the entire target site is radiated. Therefore, in the pending rejection even though the prior art of record may not explicitly describe exposure of the contrast particles to ultrasound energy to raise the temperature of their contents, Examiner has taken the view that this functionality is inherent once the particles of prior art are subject to the ultrasound energy.

Further the Declaration of Gregory Lanza has been considered but Examiner points out that the declaration is not commensurate with the scope of the claims as it appears to refer(s) only to the system described in the above referenced application and not to the individual claims of the application. Thus, there is no showing that the objective evidence that is commensurate in scope with the claims. See MPEP § 716.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 571-272-0630. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SS



RUSSELL TRAVERS
PRIMARY EXAMINER
